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BOCKELMAN, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/463,904	Joseph Phipps
Examiner	**Group Art Unit**
Bockelman	3762

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3-2-99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1, 4, 7-10, 13, 16-17 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 1, 4, 7-10, 13, 16-17 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

DETAILED ACTION

1. In view of the appeal brief filed on March 2, 1999, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(b) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 4, 7-10, 13, 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Phipps et al '739 in view of the combined teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731.

Primary reference Phipps et al '739 teaches iontophoretic devices that use hydrogel layers which, when hydrated with an aqueous solvent (column 3 lines 40-44), will contain the drug in a protonated species as well as free chloride in the aqueous solution. In essence, the resulting composition contains a drug in it's aqueous salt form as specified in the claims. The list of drugs that are included as useful in the iontophoretic delivery devices described includes the claimed drug fentanyl (column 13 line 50). The hydrogels used in the iontophoretic devices may include the drug therein in either a single layer embodiment (column 3 lines 34-39) or a two layer embodiment with a hydrogel carrier layer and a hydrogel skin contact layer with an adhesive (column 6 lines 18-20).

The examiner emphasizes that neither the use of fentanyl salts (see Theeuwes 5,232,438 reexamed claims) to achieve an analgesic effect nor the use of hydrogels aqueous solutions as reservoirs for drugs (See Petelenz et al. 4,752,285- column 16 lines 45-58) are new to the art. They were both well known at the time of applicant's invention.

While it was long recognized that fentanyl salts as well as hydrogel layers were well known constituents in iontophoretic systems, Phipps '739, like others, fail to specify the particulars of the drug concentration as defined in the claimed invention. Specifically, the prior art of record fails to specify when using the drug fentanyl, the drug concentration is maintained at a concentration above about 16 mM such that the concentration of fentanyl salt in the drug delivery reservoir is maintained at a concentration level at which the flux of the drug is independent of concentration. As can be seen from figure 2 of applicant's specification, the drug delivery rate for fentanyl, when graphed as a normalized flux versus concentration, becomes independent of concentration at a value above 16 mM such that for a given level of applied current, variations in drug concentrations will not vary the drug delivery rate, provided that the drug concentration remains above the threshold level.

While Phipps '739 and others (see Theeuwes 5,232,438 claims) were silent with respect to the concentrations of fentanyl used to achieve analgesic effects, the generalized principle of testing known drugs to determine their optimal conditions, especially that of concentration, forms the cornerstone of modern pharmacology and would have been obvious to anyone of any skill in the art who had read the Phipp's '739 disclosure. The requirement to test the fentanyl in the hydrogel reservoirs to determine the optimum conditions of operation to which achieve analgesia would have been apparent to anyone having read the Phipps patent.

Moreover, those of ordinary skill in iontophoretic delivery art and familiar with the prior art of record would have been even more directed to applicant's claimed invention since the prior art instructs the utilization of drugs in excessive amounts of that which is actually delivered to overcome problems of inadequate delivery rates/amounts and furthermore the utilization of drugs at concentrations above threshold levels for precisely the same reasons as applicant, namely to overcome the effects of competing ions.(see applicant's specification at page 25 lines 25-27) The prior art additionally teaches the benefits and hence provides the motivation of determining such values for use, such teachings including 1) making certain that a linear relationship exists between current and the drug delivered such that the amount of drug delivered was predictable (i.e. avoid over/under dosages) and 2) conserve battery power that would otherwise be wasted upon delivering competing ions as opposed to drug ions..

The Rebinder, U.S.S.R Academy of Science pp 310-327 reference provides one of the earlier teachings concerning the problems of parasitic ions (a.k.a. competing ions) and their effect upon drug delivery efficiency. The Rebinder reference is dated 1956 and was cited and applied as prior art in reexams 90/003116 and 09/001744, well before applicant's filing date and thus its teachings are considered to be well known at the time of applicant's invention. The Rebinder reference is concerned with the relationship between concentrations and drug delivery and the inconsistencies observed in past observations.

> Published experimental data on this question are inconsistent. On one hand, qualitative clinical observations suggest that under the conditions of clinical practice, the higher the concentration of the initial solution , the greater the therapeutic effect. These data are largely based on the iontophoresis of complex organic ions. On the other hand, the quantitative data of Schafferstein (1939) show that for a number of simple ions, tenfold changes in the concentration of a substance have practically no effect on the amount introduced within the limits of experimental error.

Later, in experiments on model membranes, Rebinder notes that for the drugs and membranes used the amount of drug delivered is independent of concentration, however the presence of parasitic ions, in sufficient amounts relative to the major ion, may reduce the efficiency of the major ion delivery.:

> The results obtained in the experiments in which "parasitical"ions K^+ (C^0_{KCl}) were added to the external dye solution (series Ia, Ib, IIIa, and IIIb) require no explanation. A small amount of KCl (.001N) added to a solution with a high concentration of the dye(IIIa) had no effect onp/q, while the same addition to a dilute solution (series Ia) led to a reduction in the amount of the major ion introduced.
>
> The amount of major ion introduced (p/q) falls off sharply both with an increase in the concentration of the parasitic ion (series I->Ia->Ib) and with a decrease in the concentration of the major ion (series IIIb ->Ib), i.e., in all cases in which the relative amount of the major ion in the solution was reduced.

Similar results and conclusions were reached for in vivo studies. Rebinder then tries to resolve the differences observed experimentally versus those observed clinically. Rebinder discusses the significance of parasitic ions as well as complex organic ions

> The following question is of importance in physiotherapeutic practice: how can these experimental results, which also have a theoretical explanation, be squared with the increase in the therapeutic observed with increasing concentration of the external solution.

The most important reason for the discrepancy is apparently that during clinical practice, when a pad is used, parasitic ions undergo iontophoresis along with the major ions.

It is perfectly clear that in the presence of parasitic ions, the medicinal substance will be introduced in smaller amounts than shown in Tables 120-122, and the lower the concentration of the solution, the less introduced.

Physicochemical research is not yet capable of evaluating the conviction of physicians that higher concentrations of a medicinal solution provide a greater therapeutic effect. Since this view is based on observations made on the iontophoresis of complex organic substances, questions as to the diffusion of these substances through the skin and the formation of association complexes in the solution arise.

With increasing concentration of solutions (higher than .1M, i.e., 3-4%) of complex organic substances it becomes necessary to take into consideration the possibility of association complexes forming, i.e., with the transition from a solution of a "colloidal electrolyte," as occurs, for instance dyes. In this case the process of iontophoresis becomes one of electrophoresis, and the amount of substance introduced may increase due to the increase in mass of the ion, since the linear mobility of colloidal particles is usually close to that of organic ions ($=2x10^{-4}$ cm/s). Nor should we forget the possibility of the reverse effect, namely, the decrease in the transport number in the skin as the particle size increases. The problem of how these effects are inter-related and the question of whether it is possible for association complexes to form in solutions of medicinal substances used for iontophoresis remain unresolved and require further research.

It is clear as far back as 1956 that the concepts that: 1) for concentrations regarded as normal working concentrations, iontophoresis for simple ions is independent of concentration 2) the relative amount of parasitic ions to major ions effects the delivery rate of simple as well as complex ions 3) the delivery of complex organic ions may involve other factors , and most

importantly, 4) **further research to discover the relationship between concentration and drug delivery for the various complex ions is desired.**

More recent than Rebinder are the teachings of Phipps et al USPN 5,125,894. Phipps et al discusses the relationships between drug delivery rates and drug concentration in general and how medicaments have a threshold level, above which a linear relationship exists between current levels and the amount of drug delivered. See Phipps '894 at column 10 line 41 to column 11 line16. In particular the reference states:

> In general, the amount of transport which occurs as a result of applied voltage is directly proportional to the amount of current passing through the cell. Thus, in general, if the amount of current is doubled, the rate of transport due to the electromotive force is also doubled;"

Later Phipps states:

> In practice, then, the amount of current can be utilized to control the rate of drug delivery. This can generally be done in either or both of two manners: change in the potential (voltage) applied between the active and ground electrodes; or, change in resistance to passage of current between the two electrodes. In practice , typically resistance to ionic conduction between the two electrodes decreases, as the electrolytic material begins to permeate the skin. That is, in practice there is observed a lower resistance to current passing between the electrodes, with the passage of time. Thus, over a sustained period of time, for a typical iontophoretic system with little or no extraneous ions, constant rate of target ion delivery or transport can be maintained with a lowering of voltage, at least over a given range of concentrations of drug ion in the active reservoir, when the concentration is not modified greatly and is above a threshold level determined

> by physical/chemical properties of the transported species and tissue through which transport occurs.

Phipps further states:

> In general, although rate of drug delivery is proportional to current, at a constant current, the rate of drug delivery (Rd) is independent of drug concentration (i.e. target species concentration) in the active electrode reservoir, provided that the concentration is at least above a threshold level (and little or no extraneous ions are present)

Phipps '894 dedicates the patent to various types of operation based upon these principles so as to make the drug delivery process more predictable. It's teachings are based upon those principles found in the earlier teachings of Rebinder. It is clear from the Phipps et al '894 disclosure that drug delivery predictability is essential for achieving success and that the determination, use and maintenance of drug concentration levels above a threshold levels for achieving predictability of delivery was well known. It is also apparent that the threshold levels for various drugs will vary from species to species. Therefore to have tested, determined and used the threshold levels for fentanyl and applied them to an known iontophoretic system such as that of Phipps et al '894 whether or not added intentionally added extraneous ions are present would have been an obvious optimization of parameters to those of ordinary skill in the art to sustain desired levels of drug flux. .

In further support of the examiner's contention that is was known to use excess quantities of medicaments within the drug reservoirs and specifically to do so as to increase the efficiency of delivery the examiner cites Muller et al. USPN 5,320,731 patent. Specifically at column 3 line 50 it is stated:

> If the reservoir element held, at the start of the operation, only a quantity of active principle equal to the given total quantity of active principle to be administered, and if the current was passed until this quantity had entirely diffused through the skin of the subject, the said current, towards the end of the operation, would act above all to transport ions other than those of the active principle, which would lead to excessive energy consumption and long treatment times. It is therefore preferable, in order to avoid the above drawbacks, for the quantity of active principle present in the reservoir element at the start of the operation to be in excess with respect to the said given total quantity, the said excess being able, for example, to be from approximately 2% to 1000% and more specifically from approximately 2% to 500% of this given total quantity.

From the above passage above it is clear that others recognized the benefit of starting with drug amounts in excess of up to 1000 % (10 fold) that to be delivered so as to 1) prevent competitive ions other than the drug from becoming the principle ion being transported in the late stages of drug delivery and 2) avoid expending and wasting of excess battery energy in order to deliver the amount of drug desired.

Thus, it is apparent that the prior art recognized that it was important to be able to predict the amount of drug delivered per coulombs applied and that one must experiment using the particular drug be delivered to determine it properties. It was also known at the time of

applicant's invention that in order to deliver a desired quantity of medicament to a patent , excess quantities must be provided so as to negate the effects of competing ions since efficiency decreases as drug delivery ions are depleted in the reservoir. It was also recognized that a threshold value exists wherein the effects of competing ions are no longer felt and that the amount of drug delivered become strictly dependent on the amount of current applied. Given these facts as demonstrated in the prior art and taking into consideration that Phipps '739 recognizes that fentanyl may be delivered to the body in aqueous salt forms, it would have been obvious at the time of applicant's claimed invention to use fentanyl in an iontophoresis patch and to perform the routine testing of determining the most safe and effective concentrations of drug in the reservoirs to achieve patient analgesia.

4. Claims 1, 4, 7-10, 13, 16-17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Haak et al USPN 5,203,768 (in view of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731 or in view of Newman 4,931,046). Haak et al provides working examples of fentanyl in a hydrogels which are stated to provide 25 ug of fentanyl and 5 ug of sufentanil every 5 minutes that the device is in activation. Since the device must act in a linear fashion for patentee to make this statement, it is inherent that the concentration is in the range claimed by applicant. Otherwise, the device would deliver less than the stated amount for each subsequent interval since the reservoir would be

depleted and the efficiency would continue to decrease delivering less drug per interval as time goes by. In further support of the argument of inherency it is noted that Haak et al uses a 10% by weight concentration of fentanyl in the hydrogel matrix to form the patch reservoir to which an aqueous solution (column 13 line 68 to column 14 line 1) is added. Thus, even if the gel, when hydrated, absorbs 4 times its weight in water, the concentration of fentanyl will still be 2% of the solution in the gel and still more concentrated than applicant's gel of example 1 which is and three times the minimal concentration provided by the claim. (example 1 has a concentration of 21 mg/ml of fentanyl chloride). Since applicant appears to have a common assignee and have access to these gels the examiner requests hydration data and other related material that may provide information about the drug concentrations in these examples. Haak teaches that the device is turned on during episodes of pain (i.e. turned on and off), thus a "substantial" portion of the drug remains in the reservoir when the device is intermittently turned off.

If not inherent, it would have been obvious in view of the collective teachings of Rebinder, Phipps '894 and Muller et al for reasons explained in the earlier rejection of Phipps et al '739 in view of the combined teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731 to have operated the device in the linear region for fentanyl which would inherently include at least a portion of applicant's claimed range.

Alternatively, it would have been obvious in view of Newman to have placed as much drug as desired into the Theeuwes device and limit the amount delivered by a control circuit so

that the patient may undergo self treatment for days on end. Starting at column 7 line 47, Newman describes a system in which pain killing drugs are placed in an iontophoretic system which maybe patient controlled so as to let subsequent deliveries be administered by the patient but prevent overdosages. To have implemented such a system with the Phipps et al device is provided high concentrations fentanyl so as to provide multiple dosages of pain killing medication would have been obvious.

5. Claims 1, 4, 7-10, 13, 16-17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the claims of Theeuwes et al USPN 5,232,438 (alone or further in view of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731 or in view of Newman) .

The claims of Theeuwes et al USPN 5,232,438 recite a device and a method for inducing analgesia in a patient using fentanyl salt. The examiner considers the recited concentrations in the applicant's pending claims to be inherent in the Theeuwes et al claims, for had the reservoir contained an concentration less than the requisite 16 mM, the amount actually delivered would have been less than Theeuwes et al calculated and the results of the claimed invention would have not been yielded. Although the specification of Theeuwes provides little information for such a method and device, the examiner still considers it inherent. Alternatively, it would have been apparent to one of ordinary skill in the art, that for such a device and method to be accomplished

one would have tested various concentrations of fentanyl salts to achieve the greatest efficiency and safely according to the principles of the collective teachings of Rebinder, Phipps '894 and Muller et al USPN 5,320,731

Alternatively, it would have been obvious in view of Newman to have placed as much drug as desired into the Theeuwes device and limit the amount delivered by a control circuit so that the patient may undergo self treatment for days on end.

Double Patenting

6. Claims 1, 4, 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,171,294. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the current application recites a method of drug delivery where in the concentration is maintained above about 16 mM which from applicant's specification is a composition that comprises about 1-2% fentanyl which is also the same composition as claim 7 of the 6,171,294 patent. Therefore claim 1 of the current application is merely a broader version of claim 1 of the '294 patent with the intended dosaging schemes of claim 1 of the '294 patent deleted.

7. Claims 10, 13, 16 and 17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,216,033.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 10 of the current application recites a drug delivery device wherein the concentration is maintained above about 16 mM which from applicant's specification is a composition that comprises about 1-2% fentanyl which is also the same composition as claim 7 of the 6,171,294 patent. Therefore claim 10 of the current application is merely a broader version of claim 1 of the '294 patent with the intended dosaging schemes of claim 1 of the '294 patent deleted .

Response to Arguments

The examiner first notes, without getting into the details of the references, that the concept of delivering salts forms of the drug fentanyl to a patient by iontophoresis was well known in the art at the time of applicant's invention (see claims of USPN 5,232,438). Applicant's current application claims to have made improvements on such a technique by providing in vitro experiments to determine the various circumstances which yield safe and predictable results. Presumably applicant's intend to verify such data in the future for in vivo delivery as well. It is believed that applicant's are currently, or will be, seeking FDA approval to this in the near future. The examiner notes, however, that such experimentation to determine the variables that are well defined in the art so as to provide safe, efficient and effective delivery are always determined for

FDA approval. . Applicant's current application, does little more than provide testing of fentanyl concentrations to determine which concentrations are most predictable and thus safe for delivery. The examiner thus concludes that the invention, as now claimed, is merely the result of work that is required by the FDA and would have been the work of routine experimentation and thus, on its face is obvious. Furthermore, the examiner, with the use of secondary references, has demonstrated that applicant's claimed invention would have been the mere result of applying iontophoretic drug delivery principles known to the art.

The examiner's considers it obvious to have used fentanyl at concentrations in applicant's claimed range for at least two reasons. First, it would have been obvious to load the reservoirs with as much analgesic as possible since the delivery of such drugs are most notably performed on cancer patients using control circuits to prevent overdosages, and secondly, from a mere practical standpoint, one wants to treat the patient for as long as possible and for as little cost. Applicant's have submitted references that indicated passive patches are used up to 72 hours for drug delivery. If one were to use low concentrations as well as small amounts in each reservoir as applicant considers to be the "conventional wisdom", the devices would require constant replacement leading to excessive costs. Second of all, it has been known for quite some time that competing ions present in the reservoirs lower the efficiency of drug delivery which results in turn in waste in battery power. Therefore it would have been obvious to test the devices containing the

drugs to determine which concentrations the drug has its greatest efficiency and reduced competition due to extraneous ions.

Applicant's rebuttal to the examiner's rejections are restated as the following arguments: 1) That because fentanyl is a potent analgesic one would not have not sought to use high concentrations of the drug 2) Applicant alleges that the prior art does not teach maintaining the concentration "substantially through out the total analgesic drug iontophoretic delivery period" 3) The examiner's rejections fall into the category as "obvious to try" as in the case of applicant's cited case law. 4) The prior art, specifically the Phipps '894 patent, should not be taken for what it says, but for how it should be read in light to the Phipps declaration submitted in this file 4) Despite Dr Phipps admission that each drug has a threshold value according to the species of the drug, because that value for fentanyl is higher than other drugs it should not be considered "obvious".

In regard to applicant's first argument which states that because fentanyl is a potent drug one would not have used the high concentrations recited in the claims for iontophoretic delivery, applicant offers no relevant evidence to support his allegations. To the contrary, the evidence submitted by applicant would seem support the examiner's position rather then refute it. The fact is that the references used by the examiner in rejecting applicant's claims provide specific structures (membranes for Theeuwes and circuits for Newman) and teachings directed towards limiting the delivery rate as well as the amount delivered. In contrast, applicant's claims (and

specification) are devoid of any such corresponding structures. Even more disturbing is that applicant provides no upper boundary for the concentration limit in their claimed invention. The examiner does not understand how applicant justifies their allegations that others would have limited their concentrations while applicant shows no concern in their claimed invention.

In support of his contention, applicant has submitted two pieces of evidence, namely the Yerasi and Edinboro references. However these do not provide any such relevant teachings that would instruct those in the field of iontophoretic regarding the delivery of fentanyl. The Yerasi and Edinboro references are drawn to the *passive delivery of fentanyl in its free base form* while the current invention is directed to iontophoretic delivery of fentanyl in its various salt forms.. Applicant apparently alleges that the fentanyl salt would be delivered into the patients skin in a similar fashion as by passive diffusion which would ultimately lead to overdosages of the patients as in the two references cited by applicant. . However, as was well known to those in the art at the time of applicant's invention fentanyl salts are not readily diffusible through the skin at all and would not incur the same problems as the passive delivery patches. In fact, the Alza corporation, who are the assignees of the current application, are well aware of their own patent of Gale et al USPN 4,588,580. Column 3 lines 10-15 states:

> We have discovered that fentanyl citrate, the form in which fentanyl is presently administered, has such a low skin permeability that it is not at all suitable for transdermal delivery even with the use of permeation enhancers. Instead we have found that, in order to obtain the delivery rates noted above, the drug should be incorporated in the transdermal therapeutic system in the form of the base.

Other researchers have made similar observations. Consider Ashburn et al "The iontophoresis of Fentanyl Citrate in Humans". This research paper appears to the first to describe the actual delivery of a salt form of fentanyl in *in vivo* experiments. It is noted that Ashburn uses concentrations of 3 mg/ml (see page 1147) and actually conducts experiments to determine the amount drug that is delivered by passive modes. On page 148 it is stated:

> Plasma fentanyl concentrations for each study group are shown in figures 2-7. No fentanyl was detected after passive (0.0-mA) fentanyl delivery, indicating that there was no passive drug delivery with the delivery time used in this study.

Thus, the overdosages that occurred in the references cited by applicant are unlikely to occur when using fentanyl salts in the reservoir. Furthermore, it is unclear as to exactly where in the text of the Yerasi and Edinboro references applicant extracts their "conventional wisdom" that one of ordinary skill in the art would use low concentrations. The text teaches nothing concerning limiting reservoir concentrations to any particular level but instead instructs the reader "To prevent fentanyl toxicity, both patient and care giver must be properly instructed on the use and hazards of fentanyl patches" (Edinboro et al page 742 -see Discussion). In fact, the reference appears to be more supportive of the examiner's position and seems to directly oppose those statements made in the Phipps declaration. The Edinboro reference describes patches that use 10 mg of fentanyl therein to deliver fentanyl at 100 ug/ml. The examiner further notes that Gale et al

USPN 4,588,580 use concentrations of 14.7 mg/g of fentanyl in ethanol and water to fabricate similar gels. Additionally, concern is expressed in the references that after the gels have been used they must be properly disposed of because of remaining fentanyl in the patch. Applicant states that one skilled in the art (page 12 of the brief) that "those of ordinary skill in the art would be led to using low concentrations of fentanyl in the donor reservoir and to attempting to completely deplete the donor reservoir of fentanyl at the conclusion of the total drug delivery period" . In reality, nothing could be further from the truth, the prior art shows gel loadings that last for several days and recognize that the extraction of all of the drug from the gel would be an exercise in futility since as the drug is depleted from the reservoir the concentrations eventually become so low as to be useless. See Gale USPN 4,588,580 column 7 lines 65+. "The systems originally contained approximately 200 ug/cm^2 of fentanyl and over the 24 hour useful life delivered approximately 50 ug/cm^2 resulting in a delivery of approximately 25% of the original drug loading" . **In other words 75% of the drug loaded is never delivered.**

Even the Alza corporations own commonly assigned patent to Lattin et al USPN 5,879,322 recognizes that drug is frequently leftover in the reservoir after an iontophoretic delivery takes place. The claims, in particular claims 1 and 7, are directed to a method of folding a patch containing potent narcotic (the specification identifies fentanyl as such a narcotic) so as to avoid contact with the skin.(See column 3 lines 62-65) Obviously, those skilled in the art did not

possess the same "conventional wisdom' as that argued by Phipps in the declaration of 8-3-98 that stated one would have completely depleted the patch of all drug.

Additionally, Muller USPN 5,320,731 recognizes the same to be true for iontophoresis:

> If the reservoir element held, at the start of the operation, only a quantity of active principle equal to the given total quantity of active principle to be administered, and if the current was passed until this quantity had entirely diffused through the skin of the subject, the said current, towards the end of the operation, would act above all to transport ions other than those of the active principle, which would lead to excessive energy consumption and long treatment times. It is therefore preferable, in order to avoid the above drawbacks, for the quantity of active principle present in the reservoir element at the start of the operation to be in excess with respect to the said given total quantity, the said excess being able, for example, to be from approximately 2% to 1000% and more specifically from approximately 2% to 500% of this given total quantity.

Thus, applicant's arguments as to what they allege as "conventional wisdom" is without any factual support, and to the contrary, the prior art supports the examiner's position rather than that of applicant's.. This coupled with the fact that 1) Applicant's claims have no upper limit as to the concentration of fentanyl used and 2) the references which the examiner's rejections are based use control methods (see the membranes of Theeuwes, the control circuitry of Newman and the electrode coatings of Muller et al) that would limit the amount of drug delivery amount where applicant discloses and claims none renders applicant's rebuttal totally without merit.

Regarding applicant's second argument, on page 17 of applicant's brief it is stated:

> Appellant maintains that the combination of the '739 and the '894 patents is further deficient by failing to teach the recitation in the claims that the defined concentration above 16 mM is maintained 'substantially throughout the total analgesic drug iontophoretic delivery period wherein the analgesic drug is delivered through the body surface'. This recitation renders clear that the fentanyl delivery is finally terminated even though a substantial amount of fentanyl remains in the donor reservoir. Appellant has found that this is a necessary feature of the present invention in order to avoid the substantial decrease of iontophoretic flux as fentanyl is depleted from the donor reservoir.

Earlier in applicant's brief (page 5) applicant provided the basis for their alleged support for the claim language for its meaning.

> It is important to understand that the defined relatively high concentration of fentanyl salt is maintained during the total delivery period and that accordingly, delivery is terminated before the contents of the reservoir are depleted.[7]

Applicant's footnote cites pages 12 and 13 and example 1. The examiner has carefully reviewed the cited disclosure and finds no support for the allegation that the delivery was terminated such that the 16 mM concentration was maintained until termination. Example 1 shows that the reservoirs were operated until the drug flux reached 20% of the normalized values. The examiner considers applicant to have support that the fentanyl concentration is maintained "substantially throughout the total analgesic drug delivery" since the curve of fig 2 shows that the concentrations remained high for substantially most of the 16 hour delivery period but dropped off significantly at least near the end. No where, however on the pages cited by the applicant for

support was termination ever discussed as argued by applicant. While the cited pages include the statement "to ensure a predictable flux with a particular level of applied electrotransport current, the fentanyl salt concentration in the solution contained in the reservoir should be maintained above about 11 mM, and preferably above about 16 mM", the specification does not teach any application as to how to accomplish this task and for all the reader knows it may be that the applicant envisioned providing enough drug in the reservoir to maintain the concentration at a predictable level until a set amount is delivered and then letting the letting the concentration fall off at the end of the treatment. While one may have concluded that one could have accomplished the desired result by terminating the drug delivery after the desired amount in the predictable range is delivered, this require the reader to reach outside the 4 corners of the specification in doing so. It certainly is not an express teaching of such. Applicant seems to be walking a fine line stating that the generalized statements made on pages 12 and 13 and example 1 of his specification teach a "termination" step and a similar disclosure in the Phipps '894 patent does not. Phipps states:

> Thus, over a sustained period of time, for a typical iontophoretic system with little or no extraneous ions, constant rate of target ion delivery or transport can be maintained with a lowering of voltage, at least over a given range of concentrations of drug ion in the active reservoir, when the concentration is not modified greatly and is above a threshold level determined by physical/chemical properties of the transported species and tissue through which transport occurs.

The examiner certainly cannot find any distinctions between the disclosure relied upon by applicant and that of Phipps and concludes once again that applicant's arguments and alleged distinctions are unsupported in fact and without merit.

Furthermore on page 18 of applicant's brief, applicant states:

> What the present invention seeks and what is encompassed by the quoted portion of the claim is that the device is designed so that after the last programmed dosage, the concentration of fentanyl in the donor reservoir is maintained above the defined level

The examiner challenges applicant to show where the words "programmed" ever even appeared in their specification in connection to fentanyl delivery. While the specification talks about intervals, it is unclear if these are to be continuous or how they may be implemented if they are not. Does the user turn the device on and off? The specification is written so vague as to leave gapping holes into how the devices may be implemented. Certainly there is no specifying of programmed delivery within the passages cited by applicant in support of there arguments.

Turning to applicant's citation of case law, applicant first cites In re Oetiker, 24 USPQ 2d 1443 (Fed.Cir.1992) and urges that the prior art must provide some reason, suggestion or motivation found in the prior art that would make the claimed invention obvious. The examiner notes the citation and, contrary to the case of Oetiker, the examiner is not making a non-

analogous art combination such as that of a hose clamp and garment fastener in Oetiker. Instead, the examiner combines references that are all concerned with applicant's field of endeavor, that is, the transdermal delivery of drugs by iontophoresis. The applicant also considers the examiner's rejection to be akin to the application of art in the case of Ex parte Obukowicz and urges the same standard of "obvious to try" had been applied based upon a similar generalized statement. The examiner disagrees. In the case of Obukowicz, the examiner applied two references against a claim that required the insertion of a gene encoding a toxin into bacteria and then applying the bacteria to a plant environment to combat plant insects. While the primary reference (Dean) discussed bits and pieces of the claimed invention in separate portions of the text, there is no specific teaching of combining the pieces in a manner which would meet the rejected claims. The board wrote:

> This specific statement regarding combating mosquitos using genetically engineered "natural pond microflora" is relied on by the examiner for the "suggestion" required by the aforementioned case law. However, the specific statement by Dean is not a suggestion to insert the gene into the *chromosome* of bacteria *and* apply that bacteria to the plant environment in order to protect the plant. At best, the Dean statement is but an invitation to scientists to explore a new technology that seems a promising field of experimentation The Dean statement is of the type that gives only a general guidance and is not at all specific to the particular form of the claimed invention, and how to achieve it. Such a suggestion may make an approach "obvious to try" but it does not make the invention obvious.

The courts went on to demonstrate with the teachings of other related documents how the Dean statement in the primary reference could have been directed to other inventions such as altering bacteria that grows on a pond surface and that it did not necessarily direct the reader to the invention as claimed by Obukowicz. The "general knowledge" of which the board spoke of in the case of Obukowicz was dealing with general statements that offered little or no direction to result in the claimed invention. In stark contrast, the primary references in each of the current rejections, specifically Theeuwes, Haak and Phipps specifically direct the reader to the claimed invention with the exception of drug concentrations. While the secondary references, namely Rebinder, Muller and Phipps, may be considered to teach "generalized concepts" of applying drugs by iontophoresis in the sense that the are principles that apply to all drugs to be delivered, it is clearly not the same "general knowledge" the board spoke of in Obukowitz and applicant's citation of such are not applicable to the facts concerning the application of art in this application.

Perhaps applicant's citation of Merck & Co. V. Biocraft Laboratories, Inc. , 10USPQ@D 1843,1845 (Fed Cir.1989) is of the most significance since it not only demonstrates applicant's misapplication of case law concerning applicant's third "obvious to try" argument but also directly refutes applicant's fifth argument concerning the magnitude of concentration in regard to threshold values for fentanyl as opposed to other drugs. In Merck, a question of validity before the court as to whether a commonly owned patent of the Merck Co., USPN 3,313,813 rendered obvious the later obtained 3,781,430 patent which claims a

composition of amiloride hydrochloride and hydroclorothiazide with a 1:1 to 1:10 ratio of the drugs respectively. Th earlier '430 patent includes a list of compounds including amiloride and derivatives thereof and later teaches that the are useful in combination with other classes of diuretic agents to prevent the loss of potassium which the reference identifies hydrochlorothiazide as an example. No mention of ratios of the claimed drug composition were disclosed. In determining the ultimate legal conclusion of obvious of the '430 patent over the '813, the court set forth current guidelines regarding "obvious to try" type rejections and how they applied to the Merck litigation.

> [1] An invention is "obvious to try" "where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful". In re O'Farrell, 853 F.2d 894, 903, 7, USPQ2d 1673, 1681 (Fed. Cir. 1988). This is not the situation here. The '813 patent expressly teaches "that when co-administerred with other diuretic agents known to enhance the limitation of potassium ions along with sodium ions the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents". As is apparent 'success ' is not dependent upon random variation of numerous parameters. On the contrary , the '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties.

The issue in the Merck case then turns to the magnitude of the results. The examiner considers the arguments advanced in the in the current application to be similar those in Merck. While Rebinder, Muller and the Phipps '894 patent recognized the relationship of extraneous ions and drug concentration, Phipps even in his own declaration acknowledges the principle in the first

paragraph as quoted on page 13. Then Phipps then tries to redefine his invention in terms of the threshold magnitude.

> In contrast, my discovery that fentanyl and sufentanil have a high threshold concentrations could not have been predicted from any statement made in the Padmanabhan article or, for that matter, in the '894 patent.

Essentially, Phipps argues that the magnitude of the results should render the claims nonobvious. A similar argument was raised in Merck to which the court responded.

> But, "absolute predictability of success" is not the criterion; "[f]or obviousness under 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681. When further questioned on uncertainty inhered not in the fact that an increase was to be expected, but only in the magnitude of the increase.

To which the courts further added

> The evidence at trial showed that, through requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine.

The examiner considers the current claimed invention to be nothing more than a routine testing of the drug fentanyl. Applicant's have merely taken a conventional gel, added some conventional compounds and experimented on cadaver skin to test which concentrations work best. To emphasize this point the examiner further notes *In re Aller*, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955) to which the Merck decision refers:

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances ,

> however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art.

Such is the case in the current application. As noted, applicant himself in his own declaration acknowledged that the realization of the relationship between extraneous ions and drug threshold concentrations were nothing new to the art and attributes his results in figure 1 as to the same mechanism as that explained in the Phipps '894 patent as well as the Muller and Rebinder references.

> These results show that as the fentanyl HCl concentration falls below about 6 mg/ml, a more significant portion of the applied electrotransport current is carried by ions other than fentanyl ions and the fentanyl flux is more dependent on the fentanyl HCl concentration.

Clearly there was motivation to seek out and discover these values. The examiner adds that In re Antonie, 195 USPQ 6 (CCPA 1977) as cited by applicant in his brief deals with situations in which parameters (specifically the ratio of holding tank volume to contracter area) which were not demonstrated by the examiner to be known optimizable parameters cannot be considered obvious. Such is not the case here.

Finally in regard to applicant's fourth argument as enumerated earlier above which states that the Phipp's '739 patent teaches away from the invention when read in light of the Phipps declaration, like applicant's other arguments simply has no merit. References are taken to mean what they say and are subject to an interpretation by the author filed years later. The evidence of

record overwhelming supports the examiner's position and contrary to applicant's statement that the examiner is clinging to a single statement, the prior art demonstrates that applicant did nothing more than test a known system to determine the value of a known parameter. Therefore applicant's arguments are deemed wholly unpersuasive and the examiner maintains the rejections as applied earlier in this office action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Bockelman whose telephone number is (703) 308-2112. The examiner can normally be reached on Monday through Friday from 9:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Angela Sykes, can be reached on (703) 308-5181. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3591.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0858.

MWB

August 6, 2001

Mark Bockelman

MARK BOCKELMAN
PRIMARY EXAMINER

Angela D. Sykes

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